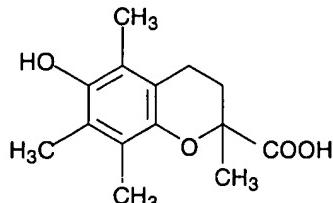


this context that **Deckner et al.** failed to teach the use of 6-hydroxy-2,5,7,8-tetramethylchroman-2-ethylenecarboxylic acid. The Examiner argued, however, that a person of ordinary skill in the art would have been motivated to employ  $\alpha$ -CHEC in the manner required in accordance with applicants' claims. The Examiner's respective argument is based on the assertions that

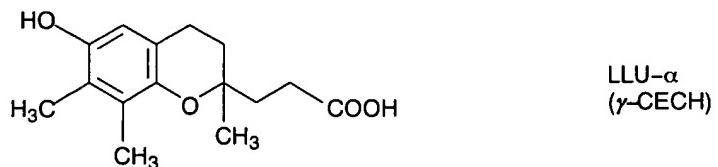
- 1) **Deckner et al.** teaches a cosmetic or topical composition comprising 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, ie.



as a free radical inhibitor;<sup>2)</sup>

- 2) **Wechter** teaches that carboxylic derivatives of tocopherols are similarly useful as therapeutic agents, particularly as antioxidants or free radical inhibitors;<sup>3)</sup>
- 3) **Wechter** specifically teaches that 6-hydroxy-2,5,7,8-tetramethylchroman-2-ethylenecarboxylic acid (LLU- $\alpha$ ) is useful as an antioxidant agent.<sup>4)</sup>

It is, firstly, respectfully noted that the name which the Examiner assigned to the compound designated by **Wechter** as "LLU- $\alpha$ " is incorrect. The respective compound has the formula set forth, for example, in col. 3, indicated lines 40 to 49, of US 6,555,575, ie.



and the name is accordingly 6-hydroxy-2,7,8-trimethylchroman-2-ethylenecarboxylic acid, or -as given by **Wechter**- 6-hydroxy-2,7,8-trimethylchroman-2-propanoic acid.<sup>5)</sup>

It is furthermore respectfully noted that the teaching of **Wechter** cannot reasonably be taken to teach or even suggest that all carboxylic derivatives of tocopherols are similarly useful as therapeutic

2) Cf. page 2, lines 16 to 20, of the Office action.

3) Cf. page 2, lines 23 and 24, of the Office action.

4) Cf. page 3, lines 3 to 5, of the Office action.

5) Cf. col. 4, indicated lines 5 to 12, of US 6,555,575. Cf. also Example 11, col. 27, particularly lines 23 and 24, of US 6,555,575.

agents, particularly as antioxidants or free radical inhibitors as asserted by the Examiner. As previously pointed out by applicants:<sup>6)</sup> While **Wechter** generically states that the  $\gamma$ -tocopherol derivatives act as antioxidants and nitrogen oxide scavengers<sup>7)</sup> it is also pointed out that the antioxidant effect of the compounds depends upon certain circumstances<sup>8)</sup> and that individual members of the class of tocopherols may exhibit different biological properties from one another despite their structural similarities<sup>9)</sup>. Before this background, **Wechter** provides that chroman compounds which include the derivative represented by applicants' formula (Ia) exhibit natriuretic properties<sup>10)</sup> which means that the compounds are capable to increase the rate of sodium excretion without contributing to significant potassium loss in mammals<sup>11)</sup>. The Examiner will also note that **Wechter** mentions, with regard to the representatives designated as "LLU- $\alpha$ " and "LLU- $\gamma$ ", that the former compound exhibits natriuretic properties and also acts as a cardio-selective free-radical scavenger<sup>12)</sup> whereas the latter compound is only effective as a natriuretic.<sup>13)</sup>

When reviewing the disclosure of **Wechter** a number of points are deemed to be of particular pertinence with regard to an asserted antioxidant or free radical inhibitor activity of LLU- $\alpha$  and other  $\gamma$ -tocopherol derivatives. On the one hand, **Wechter** generically states that LLU- $\alpha$  and other  $\gamma$ -tocopherol derivatives act

... as antioxidants and nitrogen oxide scavengers which treat and prevent high blood pressure, thromboembolic disease, cardiovascular disease, cancer, natriuretic disease, the formation of neuro-pathological lesions, and a reduced immune system response ...<sup>14)</sup>

It is, however, subsequently mentioned that the representatives designated as "LLU- $\alpha$ " exhibits natriuretic properties and is also acts as a cardio-selective free-radical scavenger whereas "LLU- $\gamma$ " is described only as being effective as a natriuretic.<sup>15)</sup> On the other hand, **Wechter** describes investigations into the reduction in the formation

6) Cf. applicants' paper dated May 10, 2005.

7) Cf. col. 1, indicated lines 6 to 15, of US 6,048,891.

8) Cf. col. 1, indicated line 30 et seq., of US 6,048,891.

9) Cf. col. 1, indicated line 44 et seq., of US 6,048,891.

10) Cf., for example, col. 6, indicated line 1 et seq., of US 6,048,891.

11) Cf. col. 4, indicated lines 28 to 31, of US 6,048,891.

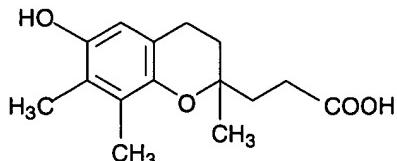
12) Cf. col. 11, indicated lines 12 to 23, of US 6,048,891.

13) Cf. col. 11, indicated lines 24 to 36, of US 6,048,891.

14) Cf. col. 1, indicated lines 20 to 29, of US 6,555,575.

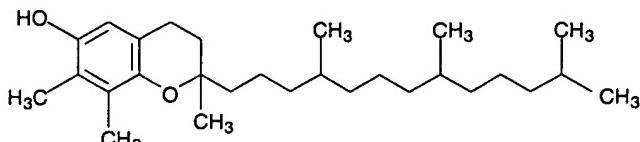
15) Ibid.

of free radicals<sup>16)</sup> in which the effects of "LLU- $\alpha$ ":

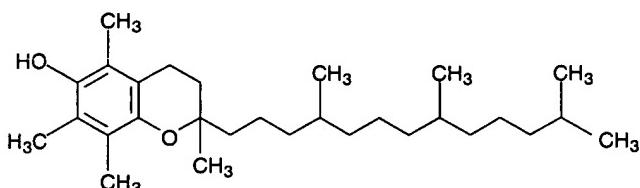


LLU- $\alpha$   
( $\gamma$ -CECH)

of  $\gamma$ -tocopherol:



and of  $\alpha$ -tocopherol:

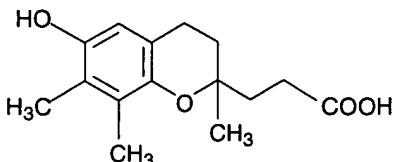


are addressed. **Wechter** state in that context that<sup>17)</sup>

[t]he results will show that breath pentane, a measure of free-radical formation in the body, is reduced in humans who received supplementation with a formulation of  $\gamma$ -tocopherol and LLU- $\alpha$  as compared to a control group which received either no supplementation or supplementation with  $\alpha$ -tocopherol

Accordingly, the presence or absence of a methyl group in the 5-position of the chroman system of tocopherols determines whether the compound is active as an antioxidant or radical scavenger, and more specifically, the antioxidant or radical scavenger effect is lost when a methyl group is present in the 5-position. In other words,  $\alpha$ -tocopherol which bears a 5-methyl substituent is inactive whereas  $\gamma$ -tocopherol which lacks the 5-methyl substituent is active.

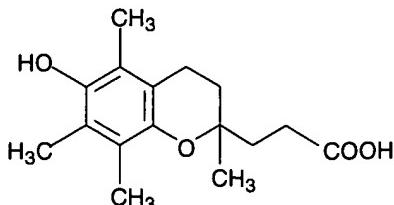
The compound of formula (Ia) which is referenced in applicants' claims differs from **Wechter's** compound LLU- $\alpha$  in that applicants' compound bears a 5-methyl group whereas **Wechter's** compound LLU- $\alpha$  lacks such a radical:



LLU- $\alpha$   
( $\gamma$ -CECH)

16) Cf. col. 35, indicated line 63, to col. 36, indicated line 25, of US 6,555,575.

17) Cf. col. 36, indicated lines 19 to 25, of US 6,555,575.



Taking the effect into consideration which the same structural change has on tocopherols the disclosure of *Wechter* when taken as a whole cannot reasonably be taken to suggest that the compound of applicants' formula (Ia) will be effective as an antioxidant or radical scavenger. It is well settled that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.<sup>18)</sup> When considered in its entirety as is necessary in a determination under Section 103(a), the disclosure of *Wechter* cannot reasonably be taken to teach or even suggest that the compound of applicants' formula (Ia) is effective as an antioxidant or radical scavenger. A person of ordinary skill in the art could therefore not reasonably expect success if the chroman-carboxylic acid of *Deckner et al.*'s compositions or methods was replaced by the compound of applicants' formula (Ia). Correspondingly, there was no motivation for a person of ordinary skill in the art to modify the teaching of *Deckner et al.* in the manner which is necessary to arrive at applicants' invention. A reasonable expectation of success, as well as some motivation or suggestion, is however needed to establish a *prima facie* case of obviousness, and the teaching or suggestion to make the claimed combination as well as the reasonable expectation of success must both be found in the prior art and cannot be based on the applicant's disclosure.<sup>19)</sup>

Moreover, the Examiner asserted that the results which were presented in Dr. Haremza's Declaration dated December 23, 2005,<sup>20)</sup> were not unexpected. In light of the foregoing considerations, applicants respectfully disagree. The data and showings presented in Dr. Haremza's Declaration further support what is mentioned by *Wechter*, ie. the fact that the usefulness of tocopherols and chroman derivatives as antioxidants or radical scavengers varies considerably. The data illustrate in particular the superior properties of the compound des-

18) *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

19) *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)

20) The original Declaration is herewith enclosed. The original is deemed to allow a better appreciation of the graphic on page 2 of the Declaration.

ignated by applicants as formula (Ia). In contrast to the showing, the prior art casts considerable doubt on the suitability of such a compound as an antioxidant.

In light of the foregoing and the attached original of Dr. Haremza's Declaration it is respectfully urged that the rejection of applicants' claims under Section 103(a) be withdrawn. Favorable action is respectfully solicited.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees, to Deposit Account No. 14.1437. Please credit any excess fees to such deposit account.

Respectfully submitted,  
NOVAK DRUCE DELUCA & QUIGG



Marvin A. Motsenbocker  
Reg. No. 36,614

1300 Eye Street, N.W.  
Suite 400 East Tower  
Washington, D.C. 20005  
(202) 659-0100

Encl.: Dr. Haremza's Declaration (original)

MAM/BAS